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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,764	09/27/2000	Joseph R. Pisegna	UCLA-P041 /2000-093-1	7433

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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/671,764	PISEGNA ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-10,20-29,31 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-10, 20, 22-29 and 31-32* is/are rejected.

7)☒ Claim(s) *21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Request for Continued Examination (RCE) filed on April 26, 2007 under 37 CFR 1.114 is acknowledged. An action on the RCE follows.

Status of the Claims

2. Claims 1-4, 6-10, 20-29 and 31-32 are pending.

Applicants' amendment and request to correct inventorship filed December 19, 2006, and amendment and Declaration of Dr. Joseph R. Pisegna filed April 26, 2007 are acknowledged. Applicants' response and Declaration of Dr. Joseph R. Pisegna have been fully considered. Therefore, claims 1-4, 6-10, 20-29 and 31-32 are examined.

Withdrawn Claim Rejections - 35 USC § 112

3. The previous rejection of claims 21 and 31 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's response at pages 5-8 of the amendment and Declaration of Dr. Joseph R. Pisegna filed April 26, 2007.

Claim Objections

4. Claim 20 is objected to because of the use of the term "one ore more agents". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 6-10, 20, 22-29 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing the efficacy of a

gastric H^+/K^+-ATPase inhibitor (PPI) in a human in need of a PPI treatment by injecting an effective amount (e.g., 0.1-10 mg/kg/hr) of pentagastrin or gastrin in conjunction with the PPI, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI, and a container containing pentagastrin or gastrin, does not reasonably provide enablement for a method of increasing the efficacy of a gastric H^+/K^+-ATPase inhibitor (PPI) in a human in need of a PPI by administering an effective amount of a pentagastrin or a gastrin in conjunction with the PPI, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI, and a container containing a pentagastrin or a gastrin, where the structure or function of a pentagastrin or a gastrin peptide and the method of administering the pentagastrin or gastrin are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1-4, 6-10, 20, 22-29 and 32 are directed to a method of increasing the efficacy of a gastric H^+/K^+-ATPase inhibitor (PPI) in a human in need of a PPI by administering an effective amount of a pentagastrin or a gastrin in conjunction with the PPI, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI, and a container containing a pentagastrin or a gastrin. The specification, however, only discloses cursory conclusions without data supporting the findings, which state that the present invention provides a method of treating pathological conditions characterized by excess gastric acid secretion, in particular the method of administering a gastrin, a pentagastrin or an analog thereof in conjunction with a PPI, which will result in increased efficacy, or a kit for the

treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI and a container containing pentagastrin (page 2, line 7-page 4, line 2). There are no indicia that the present application enables the full scope of the claim in view of a method of increasing the efficacy of a PPI in a human in need of PPI treatment and a kit for the treatment of pathology of excess gastric acid secretion as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance to enable the full scope of the claims. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses variants regarding a gastrin or a pentagastrin peptide being used with a PPI in a combination therapy to treat a human in need thereof, and the effects of various gastrin or pentagastrin peptides on the efficacy of PPI in the treatment, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

There are no working examples indicating the claimed methods in association with the variants except for administering pantoprazole to healthy humans having pentagastrin (1 μg/kg/hr) -induced gastric acid secretion and monitoring the effect of pantoprazole in the inhibition of pentagastrin-induced gastric acid secretion (Example 1). While the Declaration of

Dr. Joseph R. Pisegna shows that injection of rat gastrin I (at 250 μg/kg) and pantoprazole (at 10 mg/kg) to a mice model has enhanced reduction of gastric acid secretion as compared to mice administered only PPI (paragraphs 5-7; Fig. 1), the specification has not demonstrated oral administration of a pentagastrin or a gastrin peptide can increase the efficacy of PPI in the treatment of a patient in need of such treatment.

(3). The state of the prior art and relative skill of those in the art:

The related art (e.g., Simon *et al.* , Aliment. Pharmacol. Therap. 4, 239-245 (1990)) indicates the effect of a PPI, BY1023/SK&F 96022, on the pentagastrin (0.6 μg/h/kg)-stimulated acid secretion in healthy male volunteers. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide teachings on the effective amount of a pentagastrin or gastrin peptide by oral administration to increase the efficacy of the PPI in a combination therapy in treating human in need of PPI treatment to be considered enabling for variants.

(4). Predictability or unpredictability of the art:

The claims encompass a method of increasing the efficacy of a PPI in a human in need of a PPI by administering an effective amount of a gastrin or pentagastrin in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and a gastrin or pentagastrin peptide. However, the in vivo effects of using an effective amount of a gastrin or a pentagastrin by oral route to increase the efficacy of a PPI in a human in need of PPI treatment are not adequately described or demonstrated in the specification. While the specification describes pentagastrin is an agent that is typically to increase acid secretion (page 2, lines 9-10), and PPIs are potent inhibitors of gastric acid secretion by inhibiting H^+/K^+-ATPase

(page 2, lines 1-5); and Example 1 indicates pentagastrin (i.e., 1 μg/kg/hr) is administered continuously to induce hypersecretion in healthy subjects, and single doses of *i.v.* pantoprazole ranging 20-120 mg are found to suppress gastric acid secretion in a dose-dependent manner, the specification has not demonstrated oral administration of an effective amount of a pentagastrin or gastrin peptide can increase the efficacy of PPI in inhibiting gastric acid secretion in a human in need of PPI treatment as compared to the efficacy of using PPI alone, especially considering infusion of pentagastrin (i.e., 1 μg/kg/hr) can stimulate gastric acid secretion (see Example 1 of the specification and Simon *et al.* 1990), which has opposite effect to the PPI. The specification indicates the gastrin is preferably administered by injection and PPI is administered orally or by injection, and suggests the effective amount of gastrin/pentagastrin is 0.1 to 10 mg/kg/h. However, the specification has not disclosed oral administration of the effective amount of a gastrin or pentagastrin peptide to increase the efficacy of PPI in the treatment of excess gastric acid secretion in a human, thus the effect of oral administration of a gastrin or pentagastrin peptide is unpredictable.

(5). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to a method of increasing the efficacy of a PPI in mammal by administering a gastrin or a pentagastrin in conjunction with the PPI, or a kit for the treatment of pathology of excess gastric acid secretion, comprising a PPI and a gastrin or pentagastrin. The specification indicates the pentagastrin can be administered before, simultaneously with or after the PPI administration with the general dosages (0.1-10 mg/kg/hr) for pentagastrin, gastrin, or analogs thereof (page 2), and Example 1 demonstrates single doses of *i.v.* pantoprazole ranging

20-120 mg suppressed gastric acid secretion in a dose-dependent manner in healthy subjects under continuous pentagastrin (1 μg/kg/hr) -induced hypersecretion. However, the specification has not demonstrated an effective amount of a gastrin or a pentagastrin peptide by oral administration can increase the efficacy of a PPI in a human in need of PPI treatment as compared to the efficacy of PPI using alone. While the Declaration of Dr. Joseph R. Pisegna shows that injection of rat gastrin I (at 250 μg/kg) and pantoprazole (at 10 mg/kg) to a mice model has enhanced reduction of gastric acid secretion as compared to mice administered only PPI (Fig. 1), there are no working examples indicating the effect of orally administering a gastrin, or a pentagastrin peptide in increasing the efficacy of PPIs in a human in need of PPI treatment. Because pentagastrin has also an effect of inducing gastric acid secretion other than increasing efficacy of PPI, it is unpredictable about the effective amount of a pentagastrin/gastrin by oral administration to reduce gastric acid secretion. Since the specification does not provide sufficient teachings on the oral administration of a gastrin or a pentagastrin in conjunction with a PPI, and the in vivo effects of these peptides in increasing efficacy of PPI and inducing gastric acid secretion in a human in need of PPI treatment, it is necessary to carry out undue experimentation to find the effective amount of a gastrin or a pentagastrin by oral administration to increase the efficacy of PPI in the treatment.

(6). Nature of the Invention

The scope of the claims encompasses a method of increasing the efficacy of a PPI in a human in need of a PPI by administering a gastrin or a pentagastrin in conjunction with the PPI, but the specification has not provide sufficient teachings, nor has demonstrated the use of an

effective amount of the peptide by oral administration in conjunction with a PPI in the claimed method. Thus, the disclosure is not enabling for the reasons discussed above.

In summary, the scope of the claim is broad, the working example does not demonstrate the claimed methods in associated with variants, the effect of oral administration of the gastrin/pentagastrin is unpredictable, and the teachings in the specification are limited, therefore, it is necessary to carry out undue experimentation to find the effective amount of a gastrin or a pentagastrin by oral administration to increase the efficacy of PPI in the treatment.

Response to Arguments

Applicant indicates that the claims simply require administration of a PPI in conjunction with a pentagastrin or a gastrin. In the instant case, proton pump inhibitors (PPIs) are well known to those of skill in the art, are routinely administered to humans. Similarly, both gastrin and pentagastrin have been administered to various animals and humans, e.g. as a model system (see, e.g., Example 1) and tolerances of humans for gastrin and pentagastrin are well known to those of skill in the art. Thus, the art recognizes standard modes of administration of both PPIs and gastrin/pentagastrin. Additional evidence of the operability of the claimed invention is provided in the accompanying Declaration under 37 C.F.R. 1.132, and the Declaration discloses experiments in a standard mouse model that show that gastrin enhances the activity of a PPI (see Figure 1), and the enhanced activity is produced by injected gastrin. Furthermore, the reference by Bardan et al. (2004) Supplement to Gastroenterology, 12(4): Suppl. 2, Abstract M1439, which indicates that prestimulation of gastric proton pumps with oral PG (pentagastrin) enhances the inhibitory effect of omeprazole (a PPI) on acid secretion. This effect is mediated by a local effect of PG. Co-administraton of PG and omeprazole may be used clinically to potentiate the

therapeutic effect of omeprazole. Thus, this published scientific literature thus clearly teaches prestimulation of gastric proton pumps with oral PG (pentagastrin) enhances the inhibitory effect of omeprazole (a PPI) on acid secretion, while the pending claims are drawn to a method of increasing the efficacy of a gastric H+/K+-ATPase pump inhibitor (PP1) in a human in need of a PPI by administering a PPI in conjunction with pentagastrin or gastrin. It is well accepted law that a post-filing reference can be used to support the operability of a claimed method. Similarly the rat model discussed in Barda etal. is a standard model for the gastric secretion system and is believed to be predictive for efficacy in humans. The Examiner has failed to provide any objective evidence to refute Barda et al. Specifically, the Examiner has offered no objective basis to establish why the pentagastrin/omeprazole combination is not predictive for the combination of gastrin or pentagastrin and any other PPI. Similarly, the Examiner has offered no objective basis to establish why the rat model is not a good model for behavior of these agents in humans. Thus, the rejection under 35 U.S.C. § 112, first paragraph/35 U.S.C. § 101(a) should be withdrawn (pages 5-8 of the response).

Applicants' response and Declaration of Dr. Joseph R. Pisegna have been fully considered. Regarding the claimed method by injecting an effective amount (e.g., 0.1-10 mg/kg/hr) of pentagastrin or gastrin in conjunction with the PPI, or a kit for the treatment of pathology characterized by excess gastric acid secretion, comprising a container containing a PPI, and a container containing pentagastrin or gastrin, the argument is found persuasive and the rejection is withdrawn (see paragrph 5). However, regarding oral administration of a gastrin/pentagastrin peptide in conjunction of PPI in the treatment, the argument is not found persuasive because of the following reasons. While the specification indicates continuous

infusion of pentagastrin at 1 μg/kg/hr induces hypersecretion in healthy subjects, and gastrin is preferably administered by injection and PPI is administered orally or by injection, and suggests the effective amount of gastrin/pentagastrin is 0.1 to 10 mg/kg/h, the specification has not disclosed oral administration of an effective amount of a gastrin or pentagastrin peptide to increase the efficacy of PPI in the treatment of excess gastric acid secretion in a human. The Examiner does not dispute that the in vitro data and animal model are sufficient to establish the therapeutic utility for a compound when the correlation exists between the in vitro data and in vivo test, however, the claimed method of the instant application is directed to a method of increasing efficacy of a PPI in a human subject in need of PPI treatment, which is not directly correlated to the co-adminstration of oral pentagastrin and omeprazole in the rat model as indicated in Bardan et al., because the specification indicates gastrin/pentagastrin and the PPI can be administered preferably, the gastrin is administered by injection (e.g., subcutaneous injection), and PPI is administered orally by injection (e.g., intravenous injection), particularly, the preferred pentagastrin/gastrin dosage range from 0.1 to 10 mg/kg/hr (page 2, lines 26-31), which refers to infusion method. While Bardan et al. (2004) teach co-administration of oral pentagastrin enhances the efficacy of PPI (i.e., omeprazole) in rat model (i.e., increasing gastric pH), the specification does not disclose an oral dosage of gastrin/pentagastrin in increasing efficacy of PPI in the treatment, considering pentagastrin having an effect of inducing gastric acid secretion. Furthermore, Bardan *et al.* indicate co-administration of oral pentagastrin and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole, which also suggests undue experimentation is needed to assess the effect of pentagastrin in potentiating omeprazole in the clinical treatment. Moreover, Bardan et al. (2004) is a post filing reference,

which may be used to support the argument regarding enablement issue, but the content of the reference cannot be used as the omitted teachings for the specification at the time of filing of the instant application. Thus, the rejection for oral administration of an effective amount of gastrin/pentagastrin in conjunction with PPI in the claimed method is maintained.

Maintained Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 31 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 is indefinite because the claim has the same scope as claim 24, since claim 31 recites "said one or more agents is pentagastrin" and depends from claim 24, which recites "said PPI is dehydrated"; and claim 24, which recites "said PPI is dehydrated", is dependent from claim 21, which recites the limitation "said one or more agents is pentagastrin".

Applicant did not respond to the rejection, please see response to arguments in paragraph 3 of the previous Office Action dated October 26, 2006.

Claim Objection

7. Claim 21 is objected to because the claim is dependent from a rejected claim.

Conclusion

8. Claims 1-4, 6-10, 20, 22-29 and 31-32 are rejected; and claim 21 is objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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June 22, 2007